The kidney in Autoimmune pancreatitis : *Unmasking another face*

BY

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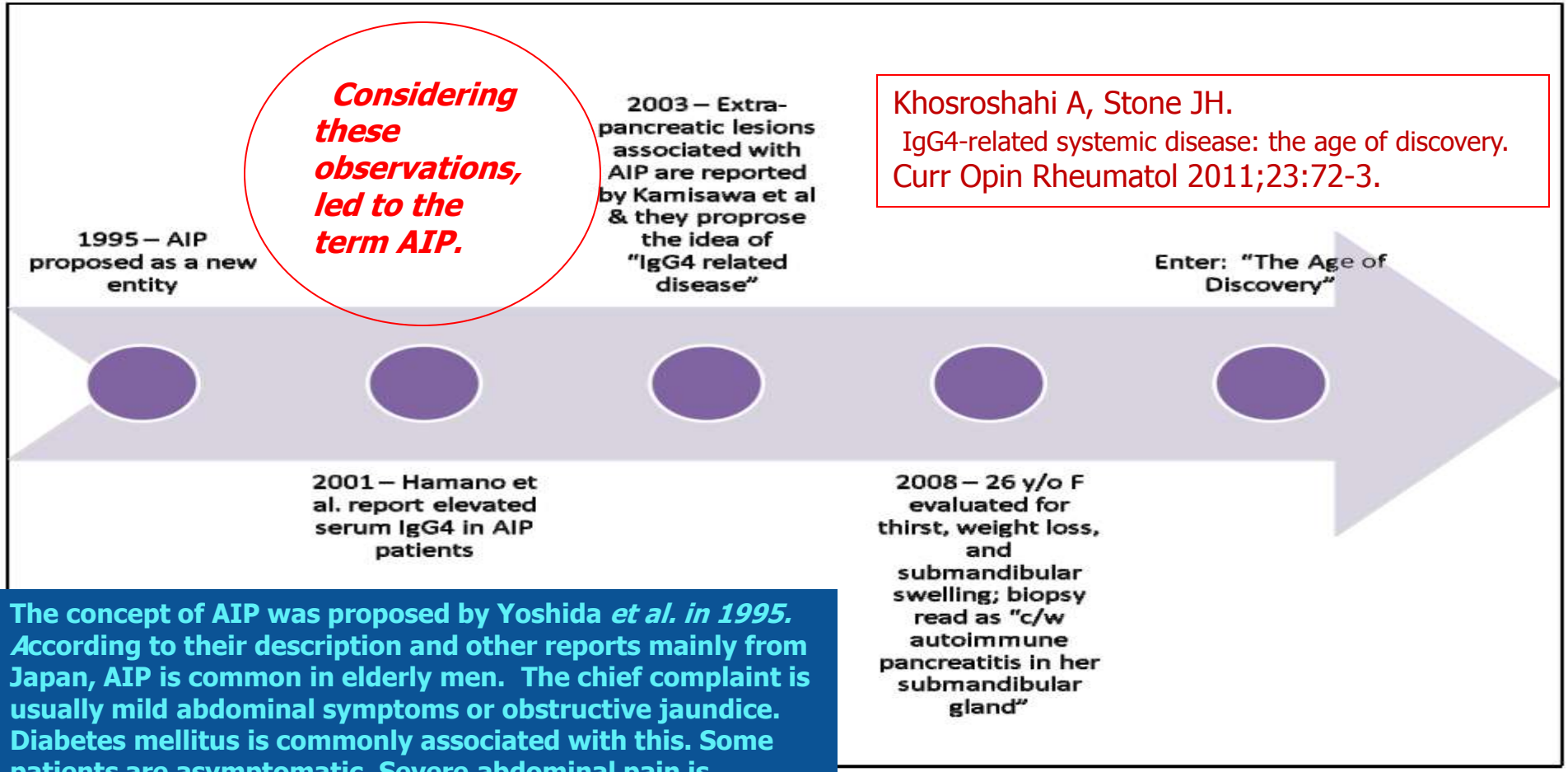
HISTORICAL PERSPECTIVE OF AUTOIMMUNE PANCREATITIS AND IgG4-RELATED DISEASES



Khosroshahi A, Stone JH.
IgG4-related systemic disease: the age of discovery.
Curr Opin Rheumatol 2011;23:72-3.

The concept of AIP was proposed by Yoshida *et al. in 1995.* According to their description and other reports mainly from Japan, AIP is common in elderly men. The chief complaint is usually mild abdominal symptoms or obstructive jaundice. Diabetes mellitus is commonly associated with this. Some patients are asymptomatic. Severe abdominal pain is exceptional. Radiologically, the affected pancreas has diffuse or focal swelling and irregular narrowing of the main pancreatic

Serology often indicated hypergammaglobulinemia, elevated IgG level .
Characteristically, serum IgG4 level is often elevated.
Notably, corticosteroid treatment is effective.

Histologically ,the condition is characterized by :a tendency to form tumefactive lesions at multiple sites; a dense lymphoplasmacytic infiltrate rich in IgG4+plasma cells; storiform fibrosis; and—often but not always—elevated serum IgG4 concentrations.

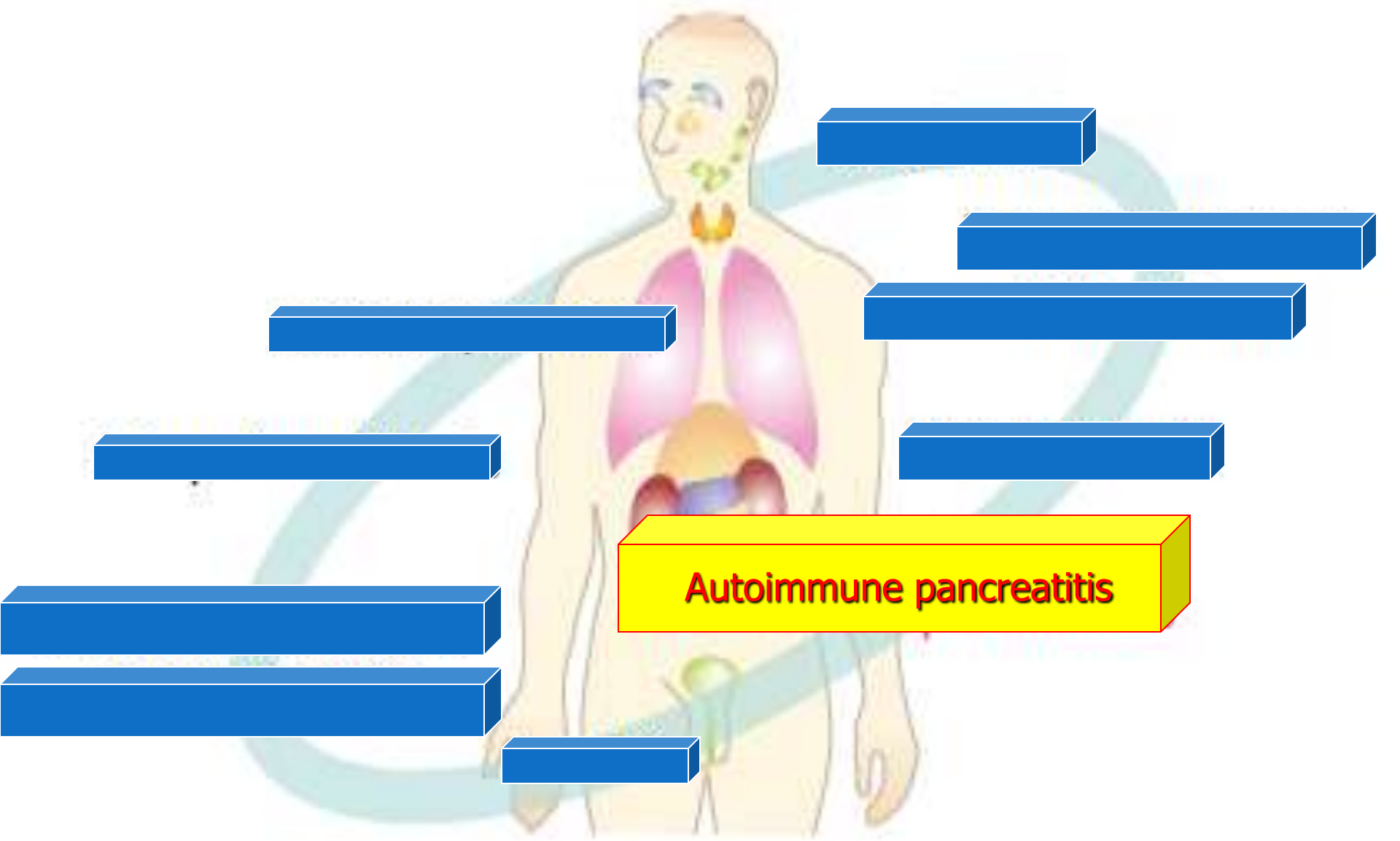
IgG4-Related Disease (IgG4-associated Disease)

- IgG4-associated sclerosing or systemic disease (ISD) is a recently established umbrella term for a range of organ abnormalities that are all associated with elevated IgG4 serum levels and/or IgG4-positive plasma cell infiltrates in different tissues.

It is difficult to ascertain the number of patients with IgG4RD because its diagnostic criteria have not yet been unified until recent days, the awareness of this disease is low, and its symptoms vary.

Kamisawa T, Takuma K, Egawa N et al.,2010

Many medical conditions that have long been viewed as conditions confined to single organs ,names embedded in the medical literature for more than a century in some cases — may now be replaced by designations that describe a key pathological feature and perhaps provide more insight into the pathophysiology



And the list is still growing

IgG4-RD accounts for some or all of the cases known previously by the following names:

- Mikulicz's disease
- Küttner's tumor
- Riedel's thyroiditis
- Eosinophilic angiocentric fib
- Multifocal fibrosclerosis
- Lymphoplasmacytic s g pancreatitis/ autoimmune panc
- Inflammatory ps mor
- Fibrosing me tis
- Sclerosing teritis
- Retrop al fibrosis (Ormond's disease)
- Peri /periarteritis
- I atory aortic aneurysm
- neous pseudolymphoma
- iopathic hypertrophic pachymeningitis
- Idiopathic tubulointerstitial nephritis
- Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
- Membranous glomerulonephritis
- Idiopathic cervical (paravertebral) fibrosis

What is common?

What is common?

Clinically

- Male
- Asian
- Age _ 50
- Tumor
- Allergy

Serologically

- Serum globin more
- Serum IgE more
- Serum IgG more

Pathologically

- Fibrosis
- Lymphoplasmcytosis
- No granuloma

Outcome

- Good Response To Steroids

Are we chasing a chameleon?

Pathogenetic issues of IgG4 related diseases

- what's wrong with IgG4?
- why common in Asians?
- autoimmune/ allergic/ infective disease?
- constitutional symptoms?
- why multifocal fibro-inflammation?

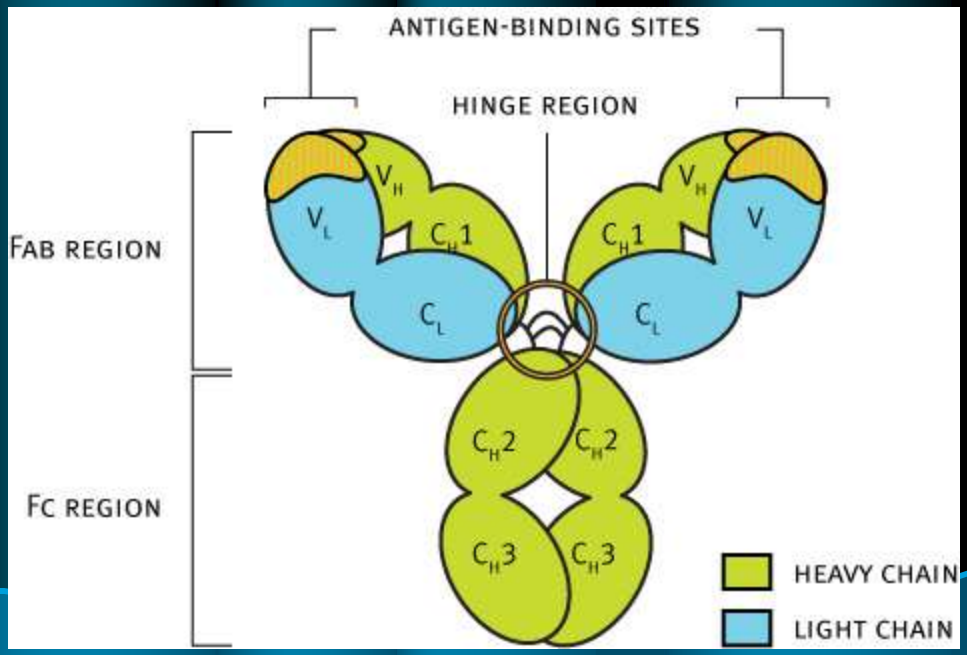
IgG4

- *what's wrong ?*

Human IgGs exist in four subclasses, IgG1, -2, -3 and -4, that have distinct structural and functional properties.
IgGs are composed of four polypeptide chains: two heavy and two light chains.

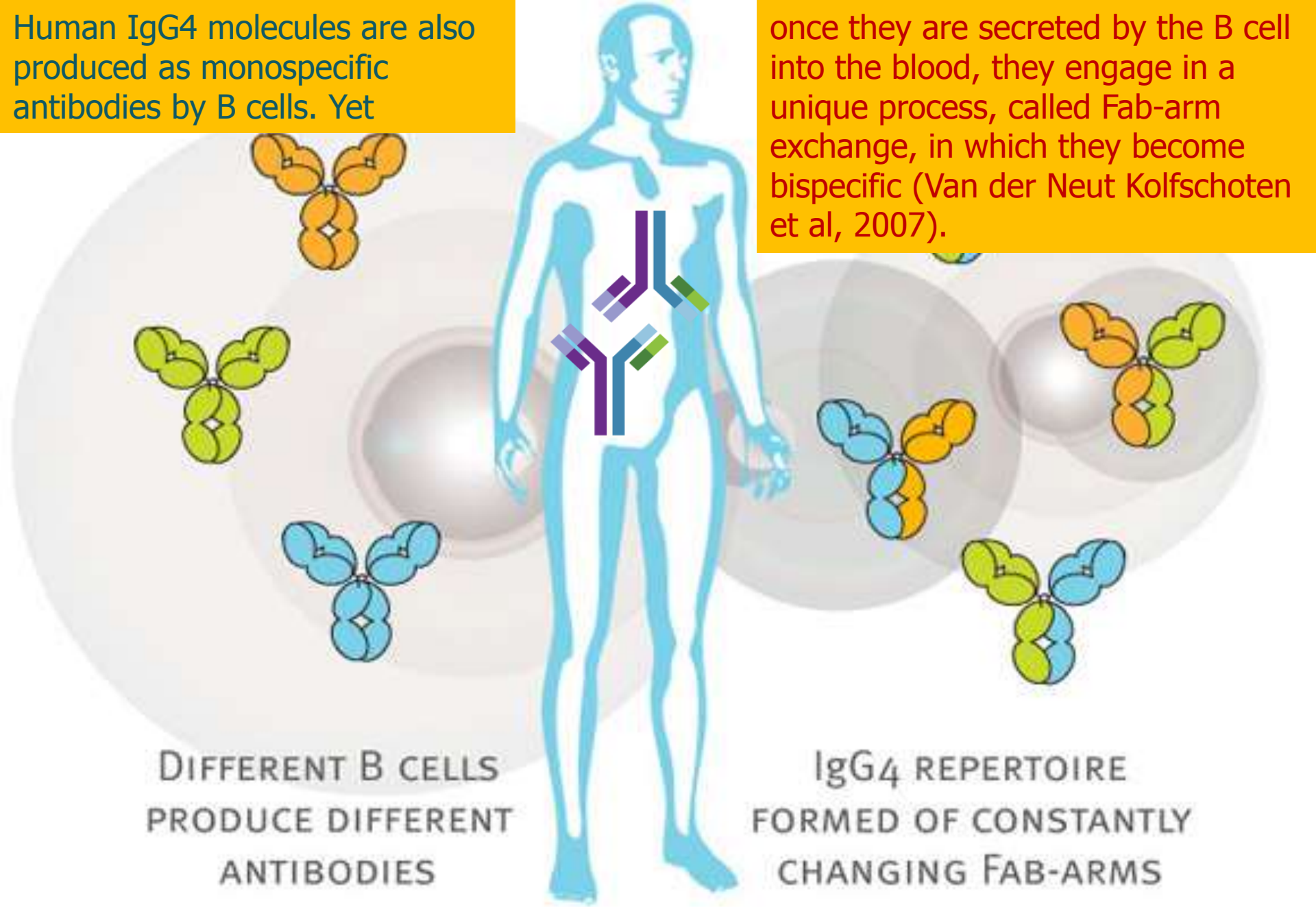
The light chains are paired to heavy chains by disulphide bonds and non-covalent interactions.
The V_L and V_H domains form the antigen-binding sites of the IgG molecule.represents an IgG Fab-arm **Fab**- (Fragment, antigen binding)

Most IgG subclasses are symmetric and contain two identical antigen-binding sites.
These antibodies are therefore monospecific (i.e. can bind to one particular epitope).



Human IgG4 molecules are also produced as monospecific antibodies by B cells. Yet

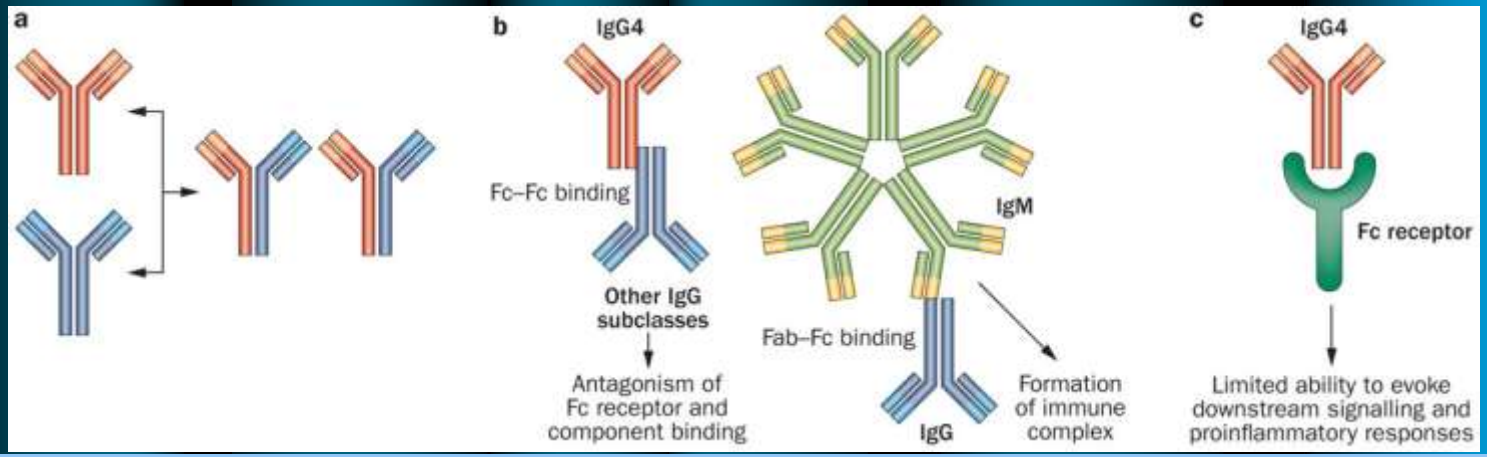
once they are secreted by the B cell into the blood, they engage in a unique process, called Fab-arm exchange, in which they become bispecific (Van der Neut Kolfschoten et al, 2007).



With modifications from D.R. Burton and I.A. Wilson, Science 2007: Vol. 317 no. 5844 pp. 1507-1508.

Figure 4 IgG4 Fab-arm exchange and Fc-dependent interactions

Yamamoto, M. *et al.* (2013) Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2013.183



a) IgG4 antibody class demonstrates an unusual characteristic termed Fab-arm exchange, which describes exchange of half a molecule (heavy chain–light chain pair) from one IgG4 for half of a different IgG4 antibody. The IgG4 molecule can thereby acquire two distinct Fab arms, each with different epitope specificity, and thus becoming bispecific.

b | IgG4 Fc regions can interact with the Fc portions of other IgG subclass antibodies (Fc–Fc binding), which could, potentially, prevent immune-complex-mediated and Fc-receptor-mediated immune responses by blocking interactions with complement proteins and Fc receptors. By contrast, IgM rheumatoid factor Fab regions recognize IgG Fc regions (Fab–Fc binding), which enables immune complex formation and leaves the IgM Fc regions accessible for Fc receptor binding.

c | The Fc region of IgG4 antibodies can also interact with various Fc receptors and complement proteins, but has minimal capacity to activate them to induce signalling; thus, these antibodies might antagonize proinflammatory responses mediated by other antibody classes via competitive interaction with these molecules.

All the 3 criteria confers anti-inflammatory properties

nature REVIEWS RHEUMATOLOGY

Four IgG subclasses; relative serum concentrations:	IgG1 > IgG2 > IgG3 ≈ IgG4
↓	
Differences in physicochemical properties	
Differences in *structure* of the 'hinge region':	• length: number of amino acids • number of inter-heavy chain disulfide bridges
↓	
Differences in the *flexibility* of the IgG molecule:	IgG3 > IgG1 > IgG4 > IgG2
↓	
Differences in biological properties	
'Fab-part' of the IgG molecule + antigen → triggering *effector functions* mediated via the 'Fc-part' of the IgG molecule.	
• Activation of complement:	IgG3 > IgG1 > IgG2 > IgG4
• Induction of phagocytosis (opsonisation) Binding to FcγR of effector cells:	FcγRI: IgG3 > IgG1 >> IgG4 FcγRII: IgG3 > IgG1 > IgG2 FcγRIII: IgG3 ≈ IgG1

Summary of the influence of the structure of the IgG subclasses on their effector functions.

Antibodies of the IgG class exert two major effector functions: activation of complement and opsonisation (i.e. the induction of phagocytosis). These effector functions, mediated via the (constant) Fc fragment are induced as a result of interaction of the antibody with its antigen via the (variable) Fab moiety.

Whether IgG4 has a direct role in the pathogenesis of IgG4RD is still unclear, and the finding of high IgG4 levels could be an epiphenomenon.?

There are two possible explanations for the overabundance of IgG4 antibodies.

First, the antibodies may behave as tissue-destructive immunoglobulins.

Second, the excess of IgG4 may simply be an over expression of these antibodies in response to an unknown primary inflammatory stimulus.

The purported tendency of IgG4 antibodies to fulfill anti inflammatory functions and the fact that disease-specific IgG4 auto antibodies have not been identified in IgG4-related disease suggest that they are a response to an inflammatory stimulus.

The high percentage of IgG4 antibodies that have become bispecific immunoglobulins through the Fab-arm exchange would render such antibodies unlikely to participate in a tissue-destructive immune response.

A major gap in the understanding of IgG4-related disease pertains to the extent of Fab-arm exchange in patients with this condition. ?????

However, the degree to which this bispecificity is fulfilled in patients with active IgG4-related disease is unclear. It is possible that a high percentage of IgG4 antibodies retain monospecificity and hence retain their potential to bind antigens and contribute to destructive inflammation.

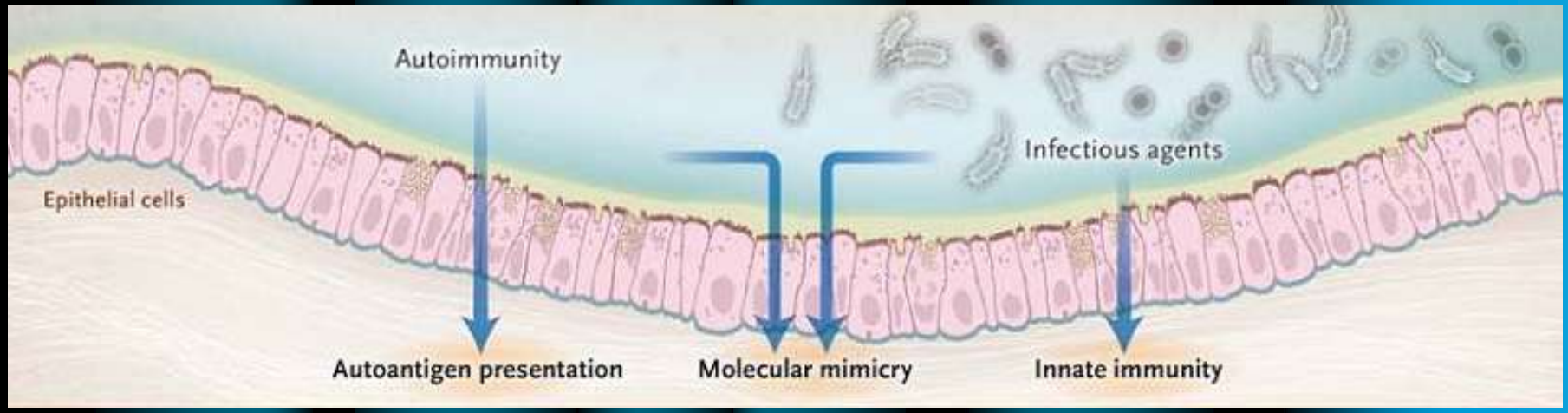
IgG4-related disease

Autoimmune ?/ allergic?/ infective disease?

IgG4 related diseases: Potential Triggers

- Male (60-80%)
- Asian
- >50 years
- **HLA DRB1*0405 (Japanese)**
- **HLA DQβ1-57 (Korean)**

H. Pylori has been linked to AIP (molecular mimicry)



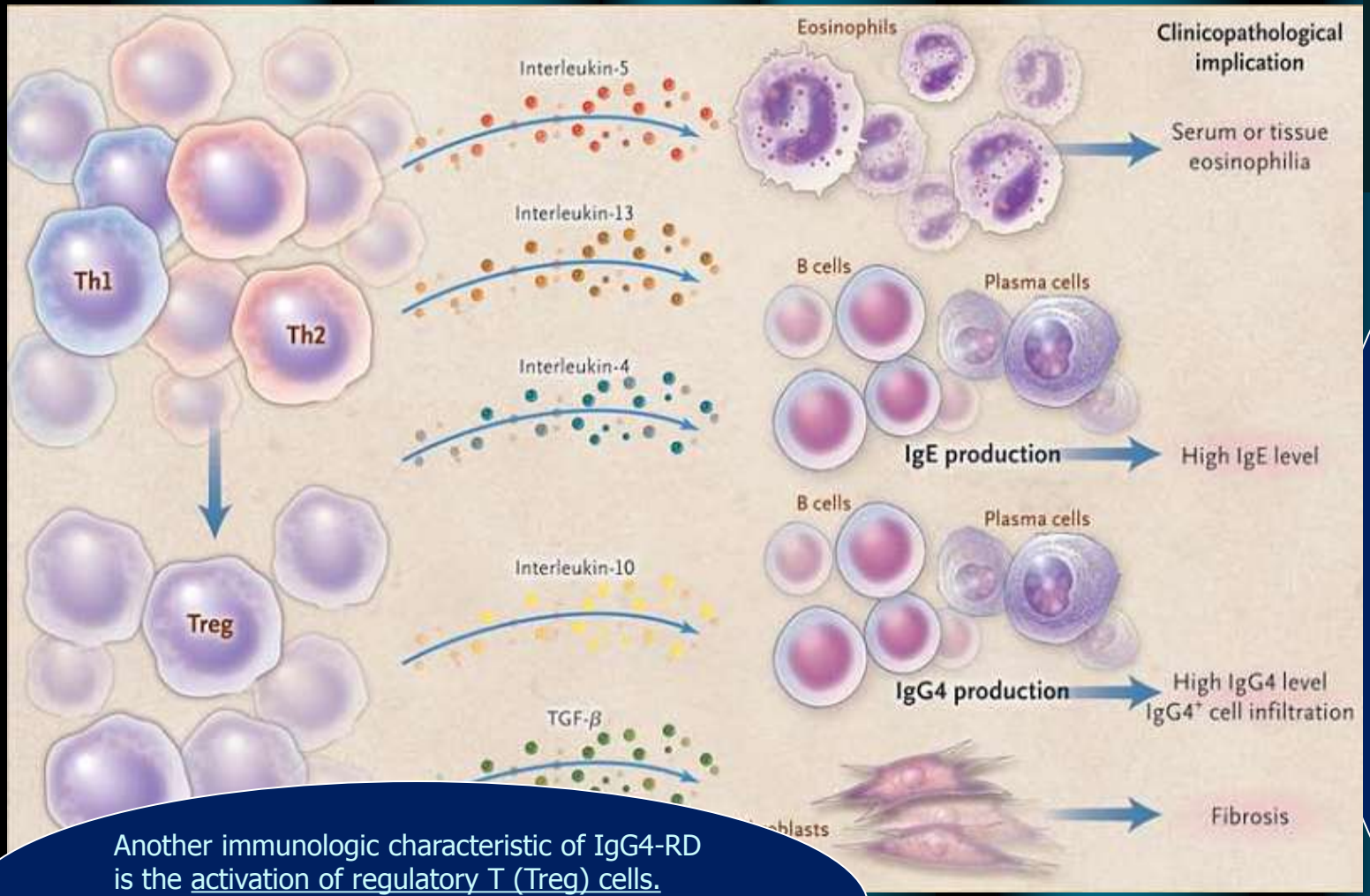
N Engl J Med 2012;366:539-51

Auto-antibodies directed against antigens expressed in various exocrine organs

Th2-cell responses are predominantly activated at affected sites in contrast to classic autoimmune conditions

IgG4 related diseases: Specific Disease Pathways

Eosinophilia & high serum IgE levels, both observed in approximately 40% of patients with IgG4-related disease, are also mediated by Th2 Cytokines mimicking allergic disease.



In addition to IL-10, which can be produced by Treg cells as well as Th2 lymphocytes,

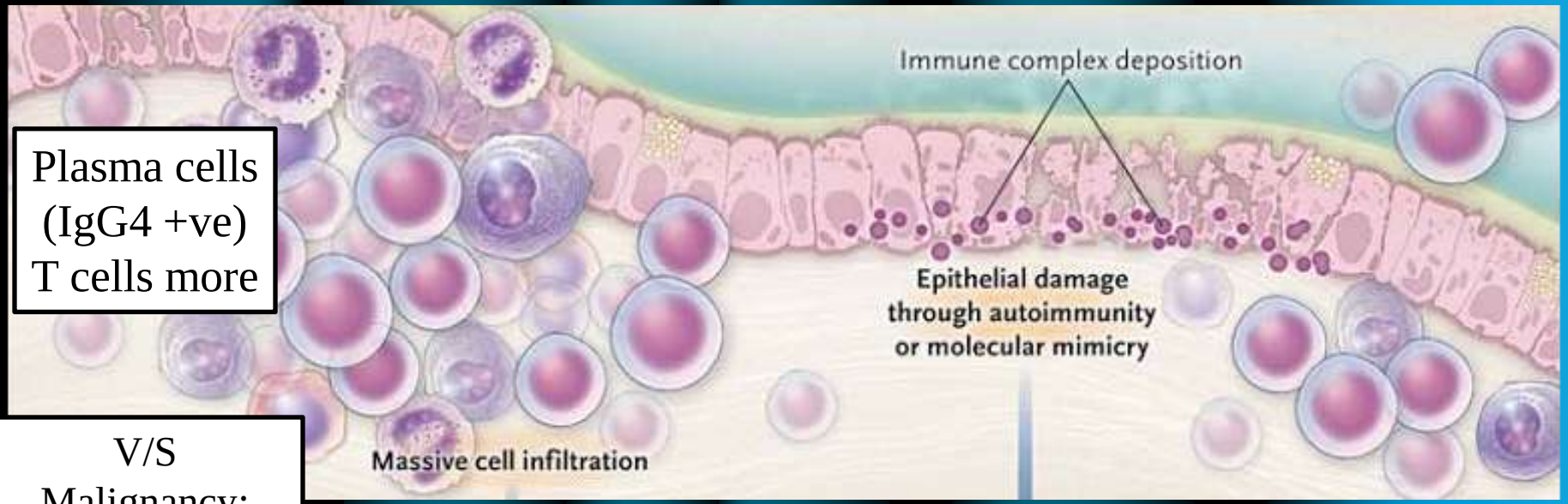
(TGF-β) appears to be over expressed in IgG4-related disease.

TGF-β may play a central role in the promotion of fibrosis in IgG4-related disease

Another immunologic characteristic of IgG4-RD is the activation of regulatory T (Treg) cells. This is an important contrast to classic autoimmune conditions, in which the function of Treg cells is impaired.

2012;366:539-51

IgG4 related diseases:
Cellular response



Plasma cells (IgG4 +ve) T cells more

V/S Malignancy: B cell Lymphoma

Tumefactive enlargement of organs or sites

It is unclear whether these organ dysfucntion are due to immune complex–mediated tissue damage or are a bystander phenomenon

So, not all IgG4 looses bispecificity

IgG4 related diseases

A new entity

New understanding of an existing disease

Multiple diseases under pathologic umbrella

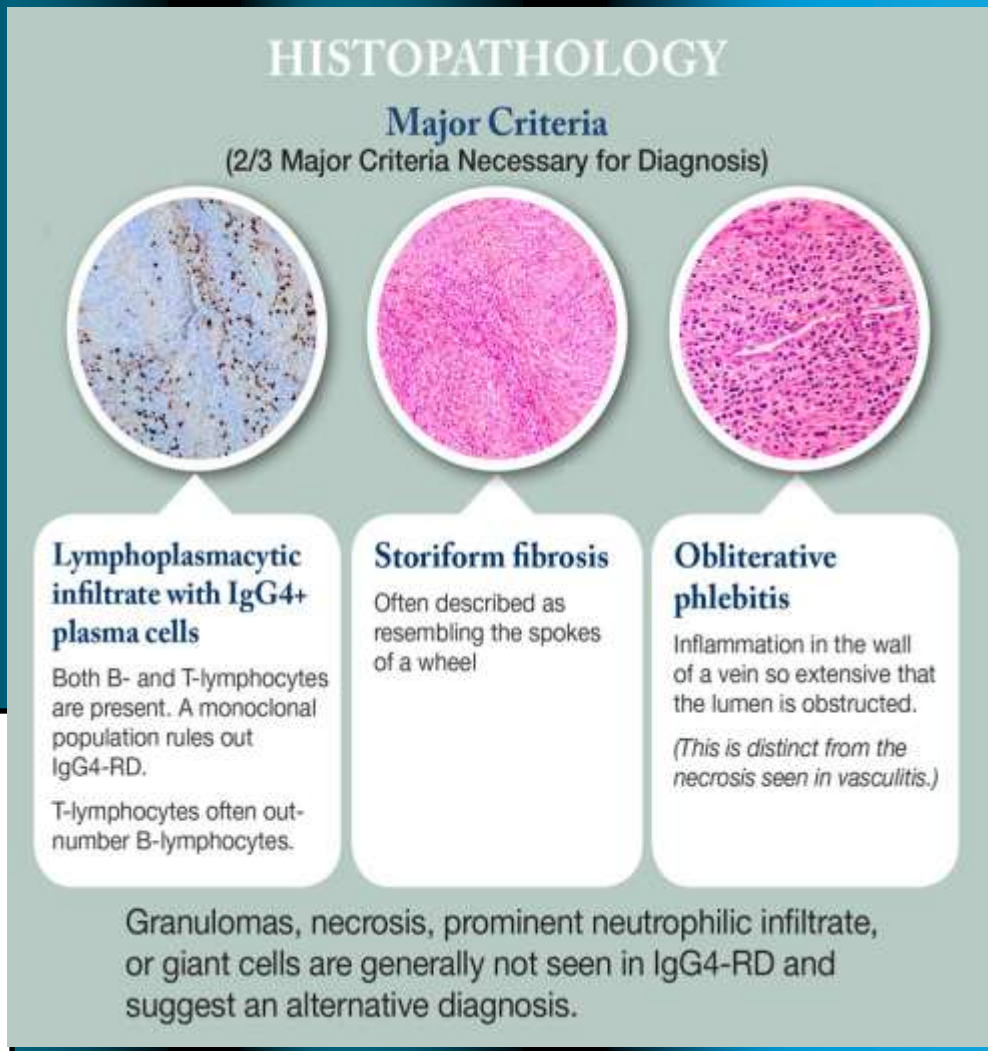
The histopathologic features of this disease bear striking similarities across organs, regardless of the site of involvement.

IgG4 related diseases

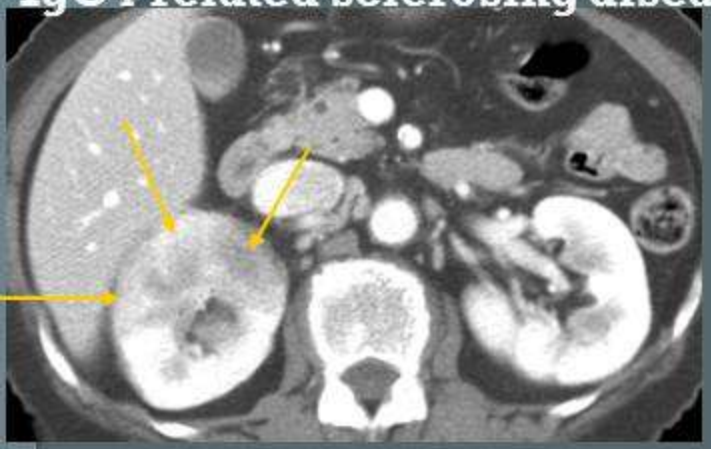
- Asian, male, >50 years
- **multi-organ involvement**
- **subacute**
- **mass-like with compression**
- lymphadenopathy
- lack of constitutional symptoms

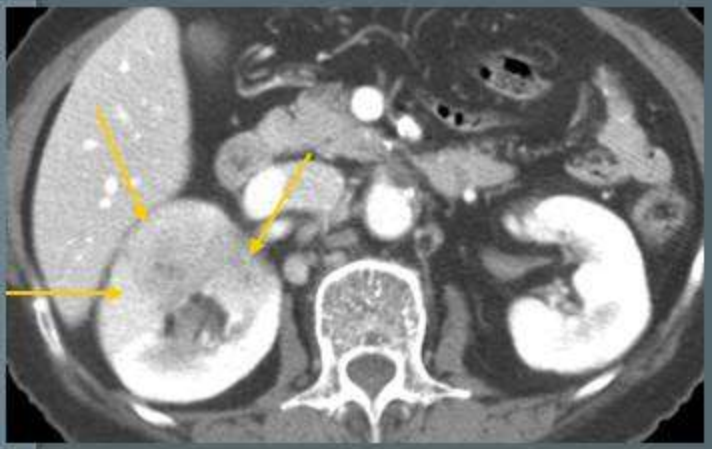
- Polyclonal hyper-gammaglobulin
- **serum IgG4 high (70%)**
- tissue IgG4/ serum IgG4>50%
- Serum IgE may be high (40%)
- allergic assocaitions (40%)
- **ANA positive (30%)**

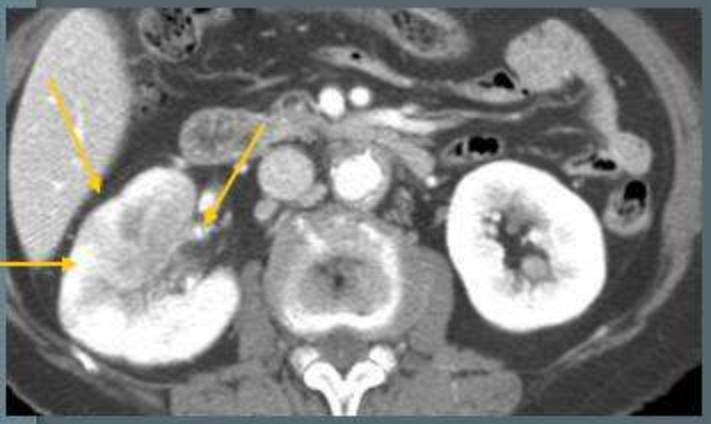
- often self-limiting; watchful waiting is prudent
- good response with steroids
- increased risk of lymphoma and other malignancy

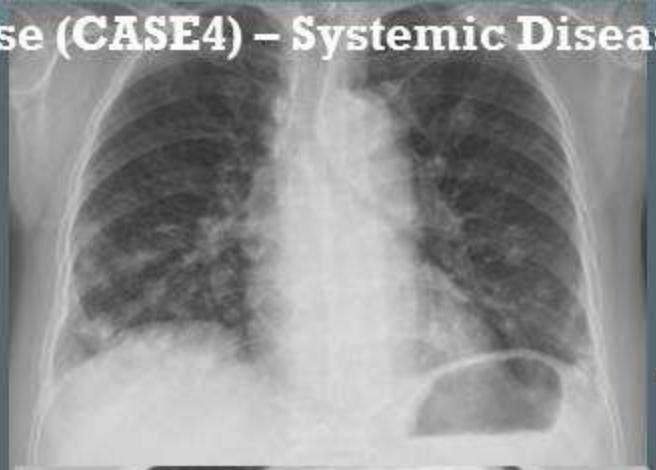


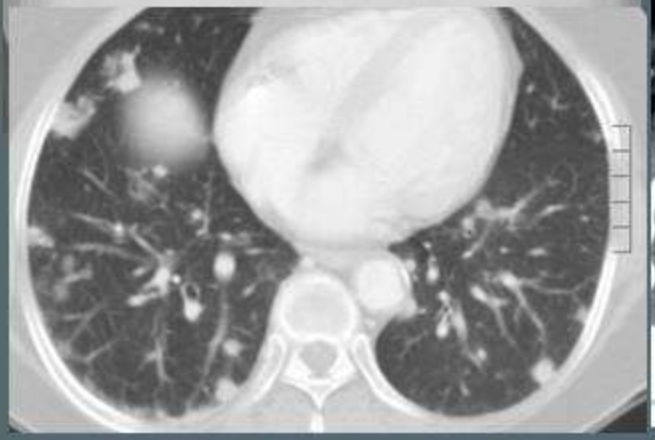
IgG4 related sclerosing disease (CASE4) – Systemic Disease pattern



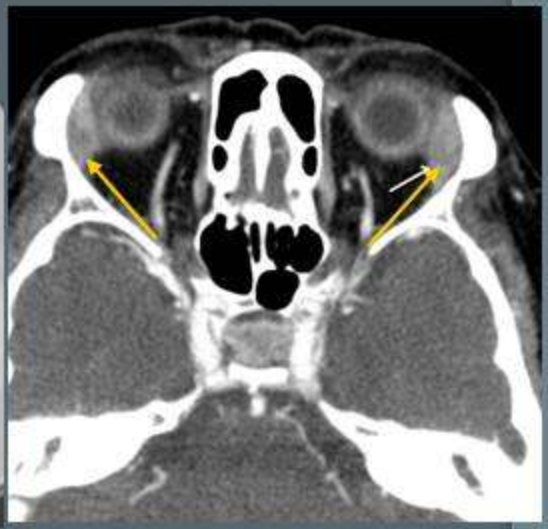








A 66-year old woman



Infiltrative heterogeneous soft tissue lesion at Rt. Kidney (ipsilateral involvement)
- poorer enhancing feature than adjacent normal parenchymae

Multiple patchy and nodular parenchymal lesions at both lower lobes of lung parenchymae

Swelling and enhancement of both lacrimal glands

IgG4 related diseases chasing chameleon

Pathogenetic issues: Demystified

- what's wrong with IgG4?
  - sine-qua-non rather than pathological
- why common in Asians?
  - HLA associations
- autoimmune/ allergic/ infective disease?
  - None; fibro inflammatory
- why no constitutional symptoms?
  - Localized depositions
- why multifocal fibro-inflammation?
  - most important cell – T reg cells
  - most important molecule – TGFb
  - most important by-product – IgG4


لا تحمل
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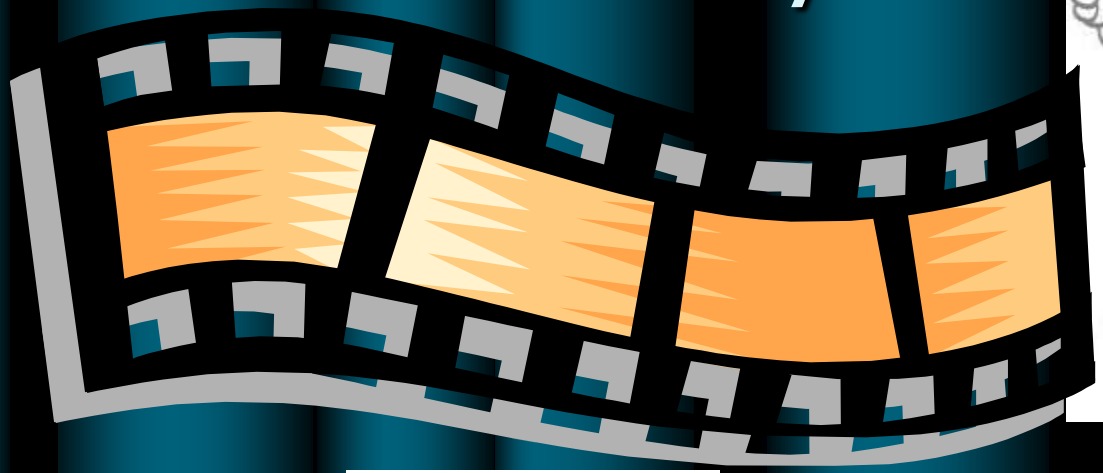
And Now Our Featured Presentation…about the kidney



IgG4-related kidney disease (IgG4-RKD) is a comprehensive term for renal lesions associated with IgG4-related disease,

- The classic renal manifestation of IgG4-RD is a tubulo interstitial nephritis (TIN) that bears all of the characteristic pathological findings found in other organs.
- Hydronephrosis , MGN , and even prostatitis can be other presentations.

- Clinically IgG4-RKD predominantly affects middle-aged to elderly men, and most patients have accompanying IgG4-related extrarenal lesions such as sialadenitis, lymph adenopathy, or type 1 autoimmune pancreatitis.

- Radiologically,

several characteristic abnormalities are often demonstrated, sometimes mimicking malignancies.

Serology usually demonstrates high levels of serum total IgG and IgG4, and high levels of serum IgE and hypocomplementemia are also frequent features.

Diagnostic criteria for IgG4-related tubulointerstitial nephritis

proposed by Kawano, *et al.*

Histology	Plasma cell-rich tubulointerstitial nephritis with >10 IgG4 positive plasma cells per hpf*
	Tubular basement membrane immune complex deposits by Immunofluorescence or electron microscopy**
Imaging	Small peripheral cortical nodules, round or wedge-shaped lesions or diffuse patchy involvement
	Diffuse enlargement of kidneys
Lab parameters	Elevated serum IgG or IgG4 levels (60% of patients)
	Hypergammaglobulinemia
	Eosinophilia
Other organ involvement	Includes auto immune pancreatitis, sclerosing cholangitis, salivary or lacrimal gland enlargement, lymphadenopathy, inflammatory mass in any organ, inflammatory aortic aneurysm, retro peritoneal fibrosis

*Mandatory criteria, **Present in 84% of cases

Corticosteroid therapy is usually quite effective, leading to amelioration of the renal dysfunction and radiological and serological abnormalities. However, as any delay in treatment may result in irreversible renal failure,

Early diagnosis and appropriate therapy are very important.

- Awareness of this condition and accumulation of more cases worldwide seems necessary.

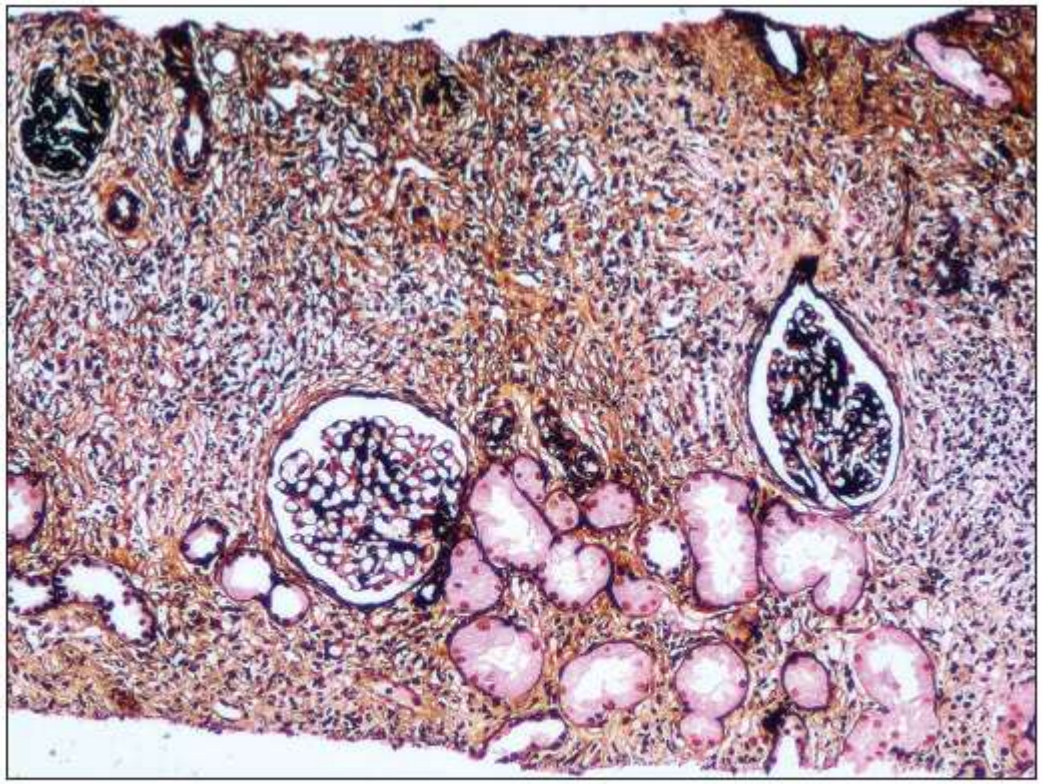


Figure 1: A dense inflammatory infiltrate along with storiform fibrosis which destroys the interstitium. There is global glomerulosclerosis and periglomerular fibrosis. silver methenamine, ×100

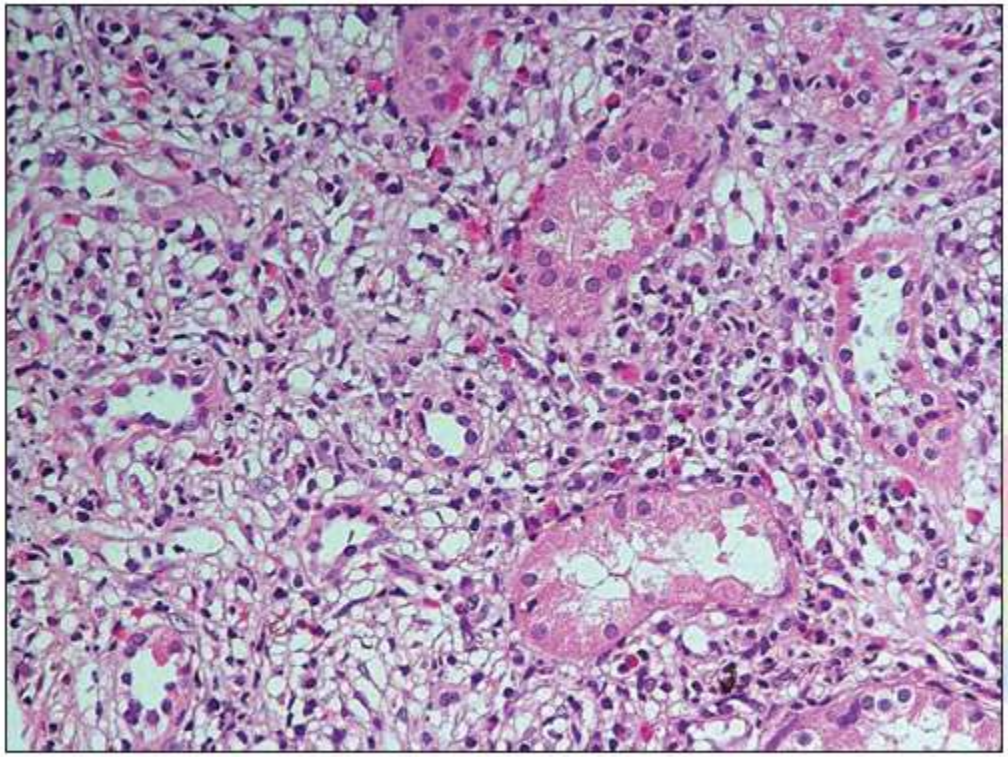


Figure 2: The tubules are separated out by fibrous connective tissue and an inflammatory infiltrate composed of lymphocytes

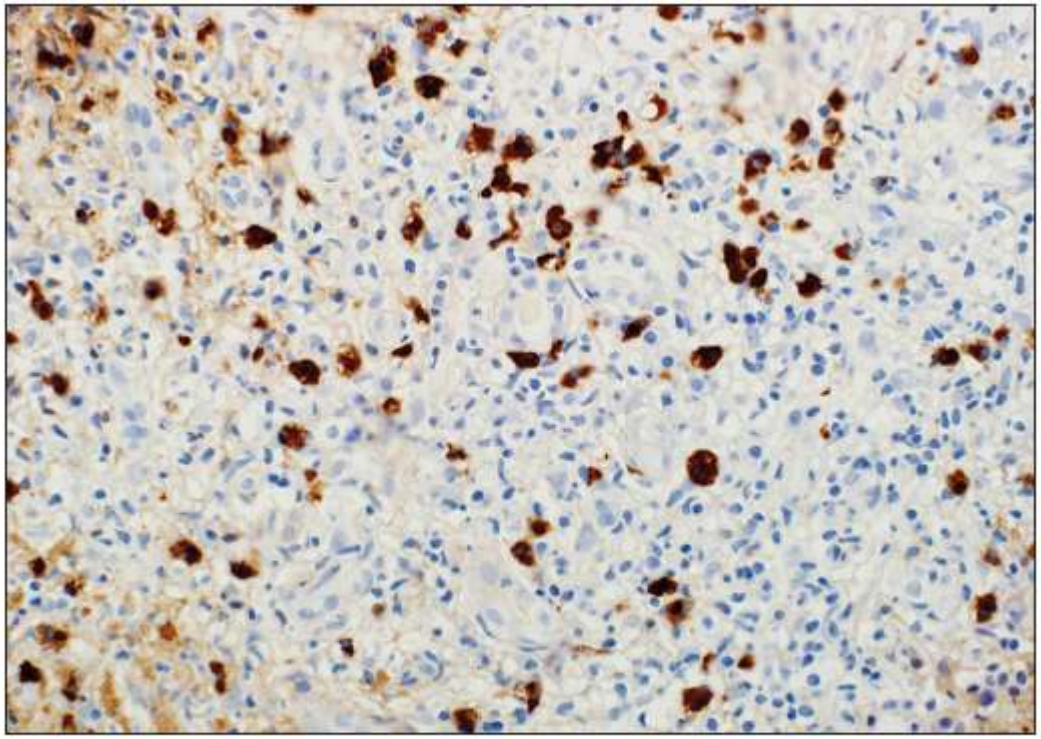
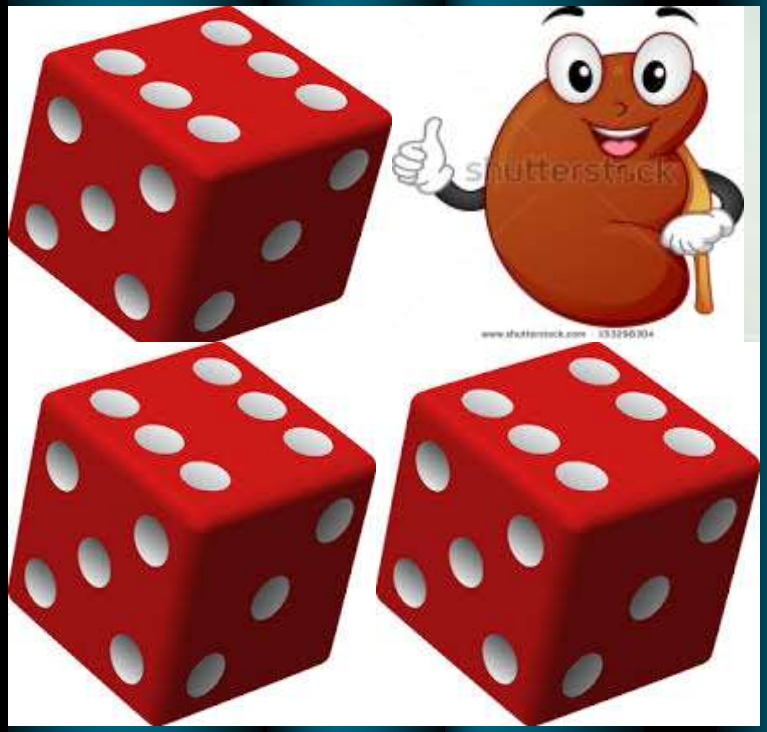


Figure 3: IgG4 immunostaining shows more than 50IgG4 positive plasmacells per high powerfield

Kidney Related IgG4 Disease is :

Another important Face of the chameleon



It should be in the differential diagnosis especially in multisystem disease presentation.

Show is over

YOU MAY NOW RELAX!